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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,711	12/12/2001	Jennifer June Brown	ENZ-57 (CIP) (C)	4374

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/042,711	BROWN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,43,49-51 and 75-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39, 43, 49-51, and 75-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 30, 2010 (hereinafter referred to as "the response") has been entered. Claims 39, 43, and 49-51 have been amended. Claims 58, 62, 63, 69, 73, and 74 have been newly cancelled and Claims 75-78 have been newly added.

Accordingly, Claims 39, 43, 49-51, and 75-78 are pending in the instant application.

The elected invention is drawn to a method for developing a therapeutic procedure in a model animal system (*in vivo* testing of a procedure).

Claims 39, 43, 49-51, and 75-78 are examined herein.

The finality of the previous Office action of March 1, 2010 is withdrawn in view of Applicants' arguments at page 5 of the response. Accordingly, Applicants are entitled to a refund of the RCE fee accompanying the filing of August 30, 2010. Applicants should request the refund in a separately filed paper. In view of the withdrawal of the finality, the Office action of March 1, 2010 will be treated as a non-final Office action and the response of August 30, 2010 will be treated as a response to a non-final Office action. Accordingly, the instant Office action is properly made final following the response to non-final of August 30, 2010. The newly added art rejections are necessitated by the amendment.

The rejection of Claims 39 and 49 under 35 U.S.C. 103(a), as being unpatentable over Xie et al. (1998, Virology 244: 513-520) is **withdrawn** in view of the amendments to the claims removing HCV as the infecting human viral pathogen.

The objection to Claims 62 and 73 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of the claim from which it depends, is **withdrawn** in view of the cancellation of these claims.

The double patenting warnings pertaining to Claims 58, 69, and 74, indicating a potential objection under 37 CFR 1.75 as being substantial duplicates of 51, 58, and 63, is **withdrawn** in view of the cancellation of Claims 58, 69, and 74.

Priority

Applicant's claim for domestic priority under 35 U.S.C. § 120 is acknowledged. However, the non-provisional application 08/876,635 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for Claims 39, 43, 49-51, and 75-78 of this application. The earlier-filed application does not disclose an animal model as recited in the instantly claimed methods. Accordingly, the effective filing date of the instant application is July 16, 1999, the filing date of Application No. 09/356,293.

Applicants did not address this issue in the response of August 30, 2010, nor in the prior response of January 22. 2010, as noted in the Office action of March 1, 2010 (pages 2-3), nor in the prior response of December 23, 2008, as noted in the Office action of 7/22/09 (page 3). It is assumed that Applicants acquiesce to the priority issue.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 39 and 43 stand rejected and Claims 75-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for developing a therapeutic procedure. The claimed method involves infecting a *Tupaia belangeri* with a human viral pathogen, wherein said pathogen is HIV or HBV, carrying out a potential therapeutic procedure on the infected animal, and evaluating the effect of the potential therapeutic procedure on disease manifestations (or clinical manifestations) caused by the human viral pathogen in the infected animal. Certain claims recite the evaluation of specific disease manifestations, including the presences or quantity of a component of the viral pathogen. The component may be viral RNA, a viral protein, or a serum antibody that specifically reacts to a component of the viral pathogen. Thus, a variety of indicators of hepatic disease or HIV infection may be evaluated, as recited in the claims.

The specification fails to provide a written description of a *Tupaia belangeri* infected with HIV and having a disease phenotype marked by the presence of a viral RNA, protein, or serum antibody that reacts to a component of HIV, or any other disease phenotype, such that the infected animal would model the human infection and disease sequelae. Animal models of infectious disease are notoriously unpredictable for reasons of record, and therefore one of skill in the art would not know if a *Tupaia belangeri* infected with HIV would exhibit disease characteristics analogous to the disease characteristics observed in humans. The phenotype of an HIV-infected *Tupaia belangeri* is not known and is not described. Claims that recite evaluation of specific parameters, such as the presence of a viral RNA, protein, or serum antibody that reacts with a component of HIV, require an infected tupaia that has a phenotype exhibiting presence of a viral RNA, protein, or serum antibody to HIV, but the specification does not describe such an animal. Because disease phenotypes are unpredictable in animal model systems, extensive characterization of the animal model is required before it can be used in a screening protocol to identify therapeutic procedures. Because disease manifestations are not predictable, the

disease characteristics of the infected animal must be determined experimentally. However, the instant specification provides no description of the phenotype of an HIV-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as indicators of viral disease caused by HIV.

The evidence of record shows that animal models of human infectious disease are notoriously unpredictable (see Lewis et al., 1995). Numerous attempts to produce or identify a suitable animal model for HIV infection have met with limited success (Lewis et al., 1995). The prior art shows that macaques, baboons, chimpanzees, pig-tailed macaques, and gibbons are susceptible to infection with HIV. Thus, the nonhuman host range is extremely limited. Moreover, the pathogenesis varies substantially from species to species. Lewis et al. (1995) discuss the many problems that exist with regard to the disease characteristics displayed by the best animal models for HIV infection. Furthermore, animal models require extensive characterization before they can be used in pre-clinical testing (see Lewis et al., page 149, column 1, paragraph 1). Intensive effort has been applied to developing animal models of HIV and other viral diseases with extremely limited success.

The instant specification only discloses two model systems; one *in vivo* (HBV-infected *Tupaia belangeri*) and one *in vitro* (HIV-infected *Tupaia belangeri* cells). *Tupaia belangeri* were shown to be susceptible to infection by HBV and their peripheral blood lymphocytes (PBLs) to infection by HIV in culture. No HIV pathogen was examined for its capacity to infect *Tupaia belangeri in vivo*. With regard to Claim 43, the specification makes no mention of carrying out an oral tolerization protocol on an HIV-infected tupaia and the specification does not describe oral tolerization of an HIV-infected tupaia. Furthermore, given the open claim language, genetic modification may be used to develop a *Tupaia belangeri* strain that is rendered susceptible to infection by HIV. The claims encompass genetically modified *Tupaia belangeri* animals, but the specification does not disclose any genetic modifications that could be made to render an individual *Tupaia belangeri* susceptible to infection by HIV or to produce a

model that more accurately reflects the disease manifestations observed in infected humans. In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. In this case, only one animal model (the HBV-infected *Tupaia belangeri*) has been tested to investigate possible disease manifestations that may be exhibited over the course of an infection. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, no other embodiments have been sufficiently described by relevant identifying characteristics. This limited information regarding the claimed embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of an HIV-infected *Tupaia belangeri* disease model required by the claims, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed methods.

With regard to the claimed methods for developing a therapeutic procedure, adequate written description is not provided in the as-filed specification. The as-filed specification does not describe a method for evaluating a therapeutic procedure with the steps set forth in the present claims. Even as relates to the disclosed *Tupaia belangeri* models, no *in vivo* screening methods are disclosed as such. With regard to HIV, only an *in vitro* model system is disclosed, and there is no contemplation of carrying out the steps of the presently claimed method using a *Tupaia belangeri* infected with HIV. The absence of any written description of screening methods as claimed cannot be remedied by oral tolerization experiments carried out with HBV-infected *Tupaia belangeri*, as the claims are much broader in scope than what is described in that experiment. Thus it is concluded that the written description requirement is not satisfied for the claimed methods.

While the skilled artisan would know the disease symptoms displayed by humans for any given human viral pathogen, the artisan would not know the disease symptoms displayed by any given *Tupaia belangeri* animal in response to an infection with HIV. As the art of record shows, different animal

species exhibit different symptoms and most do not exhibit the same symptoms seen in humans. As Lewis et al. shows, animal models require extensive characterization before they can be used in pre-clinical testing and the instant specification provides **no** information with regard to disease phenotypes for *Tupaia belangeri* infected with HIV. Given the unpredictability in the art, for reasons of record, the specification provides no guidance as to what symptoms would be exhibited by a *Tupaia belangeri* infected with HIV.

At page 6 of the response, Applicants assert that Claim 39 is fully described in the specification since step c), "evaluating the effect of said potential therapeutic procedure on disease manifestations caused by said human viral pathogen in said infected animal" is fully described in the specification, e.g. at Example 3 at pages 20-22, describing evaluation of HIV disease manifestations by measuring p24 in infected *Tupaia* peripheral blood lymphocytes. On the contrary, the claims require the use of an HIV-infected **animal** and therefore an animal with a disease phenotype is required in order to carry out the claimed screening method. The specification, however, does not disclose an HIV-infected *Tupaia belangeri* and does not disclose the phenotype of such an animal. Therefore, there is no evidence that such an animal would exhibit the same disease manifestations exhibited by HIV-infected humans and therefore there is no evidence that such an animal would actually model the human condition. Absent an animal that does actually model the human condition, one of skill in the art could not use such an animal is a screening method to develop a therapeutic procedure. These screening methods require an animal that models the human disease. No such animal is described in the instant specification.

At page 6 of the response, Applicants allege that assays for other HIV disease manifestations are well known and therefore the specification need not disclose them. On the contrary, the HIV disease manifestations exhibited by *Tupaia belangeri*, if any, are not known at all. Only disease manifestations in humans were well known at the time of filing, but there is no evidence at all that HIV-infected tupaias

would model the human disease and exhibit the same disease manifestations. The disease manifestations of tupaias exposed to HIV, if any, were not known and the specification does not describe them either.

At page 6 of the response, Applicants allege that the specification does contemplate the presently claimed method steps at page 9 of the specification where it states that "[t]his aspect of the present invention provides a small animal model for infection by human retroviruses that can be used for screening therapeutic regimens for blocking viral replication in this host." However, while the specification broadly contemplates using a *Tupaia belangeri* as a small animal model for screening therapeutic regimens, it never mentions carrying out an oral tolerization procedure on an HIV-infected tupaia, as set forth in Claim 43. Likewise, the specification does not describe evaluating the various parameters set forth in Claims 75-78 for an animal exposed to HIV. The specification does not mention any particular disease manifestations that would be evaluated in accordance with the presently claimed method steps for an animal exposed to HIV. There is no description of an HIV-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as indicators of infection caused by HIV.

Thus, in the absence of a description of HIV-infected *Tupaia belangeri* that exhibit disease characteristics analogous to the disease manifestations seen in humans, one of skill in the art would not find that Applicants were in possession of an HIV-infected animal model suitable for the therapeutic screening protocol claimed.

Enablement

Claims 39 and 43 stand rejected and Claims 75-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic screening methods that use *Tupaia belangeri* infected with HBV in a method for developing a therapeutic procedure, does not reasonably provide enablement for therapeutic screening methods that use HIV-infected *Tupaia*

belangeri. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for developing a therapeutic procedure, wherein the method involves evaluating a variety of indicators of viral infection as recited in the claims. The claimed method involves infecting *Tupaia belangeri* with a human viral pathogen, wherein said pathogen is HIV or HBV, carrying out a potential therapeutic procedure on the infected animal, and evaluating the effect of the potential therapeutic procedure on disease manifestations caused by the human viral pathogen in the infected animal. Certain claims recite the evaluation of specific disease manifestations, including the presence or quantity of a component of the viral pathogen, particularly viral RNA and viral protein, and the presence of a serum antibody that specifically reacts to a component of the viral pathogen. Thus, a variety of disease manifestations may be evaluated, as recited in the claims.

The specification fails to provide an enabling disclosure for the use of a *Tupaia belangeri* infected with HIV and having a disease phenotype analogous to the disease characteristics seen in humans, such that the infected animal would model the human infection and disease sequelae. Animal models of infectious disease are notoriously unpredictable for reasons of record, and therefore one of skill in the art would not know *a priori* if a *Tupaia belangeri* exposed to HIV would become infected and exhibit disease characteristics analogous to the disease characteristics observed in humans. The phenotype of an HIV-infected *Tupaia belangeri* is unpredictable. Claims that recite evaluation of specific parameters, such as viral RNA, viral protein, or serum antibodies, require an HIV-infected *Tupaia belangeri* individual that exhibits those infection markers, but the specification does not describe such an animal. Because disease phenotypes are unpredictable in animal model systems, extensive characterization of the animal model is required before it can be used in a screening protocol to identify therapeutic procedures. Because disease manifestations are not predictable, the disease characteristics of

the infected animal must be determined experimentally. However, the instant specification provides no guidance regarding the phenotype of an HIV-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as disease manifestations caused by HIV infection of tupaias.

The instant specification only discloses two model systems: one *in vivo* (HBV-infected *Tupaia belangeri*) and one *in vitro* (HIV-infected *Tupaia belangeri* cells). *Tupaia belangeri* were shown to be susceptible to infection by HBV and their peripheral blood lymphocytes (PBLs) to infection by HIV in culture. HIV was not examined for its capacity to infect *Tupaia belangeri in vivo*. Furthermore, given the open claim language, genetic modification may be used to develop a *Tupaia belangeri* strain that is rendered susceptible to infection by HIV. The claims encompass genetically modified *Tupaia belangeri* animals, but the specification does not disclose any genetic modifications that could be made to render an individual *Tupaia belangeri* susceptible to infection by HIV or to produce a model that more accurately reflects the disease manifestations observed in infected humans. Animal models of human infectious disease are notoriously unpredictable as evidenced by the numerous attempts to produce or identify a suitable animal model for HIV infection (see Lewis et al., 1995). Lewis et al. (1995) discuss the many problems that exist with regard to the disease characteristics displayed by the best animal models for HIV infection. None of the animal models exhibit the hoped-for characteristics as outlined in Box 1, page 144. Thus, despite an enormous amount of data on the HIV virus and its role in causing AIDS, and despite intense efforts to generate an adequate animal model, significant deficiencies remain.

Given the lack of specific guidance in the specification with regard to HIV-infected *Tupaia belangeri*, the limited working examples disclosed, and the unpredictability in the art for developing animal models of human infectious diseases, particularly HIV models, one skilled in the art would have been required to engage in undue experimentation to produce HIV-infected *Tupaia belangeri* animal

models that accurately model the human disease caused by HIV. Animals exhibiting the hoped-for disease manifestations that correlate to the human disease are required for the claimed screening methods.

At page 7 of the response, Applicants assert that the specification is enabled for the claimed use of developing a therapeutic procedure in an HIV-infected *Tupaia belangeri* by evaluating the effect of a potential therapeutic procedure on disease manifestations, for example reducing viral load, since Example 3 discloses a test for p24 production in infected cells. Applicants allege that, since the specification describes successful infection of peripheral blood lymphocytes with HIV and maintenance of that infection for at least two weeks, the skilled artisan would understand that there is a reasonable expectation that a *Tupaia belangeri* could be infected *in vivo*, such that a potential therapeutic procedure could be carrried out with such an animal. On the contrary, *in vitro* systems of HIV-infected cells are not predictive of *in vivo* responses and effects, and do not predict the disease manifestations that may or may not arise if an *in vivo* infection is established. For example, cell culture systems are not subject to the *in vivo* immune system of an animal and therefore are not affected by the immune response of the animal. One of the primary functions of the immune system is to clear viral infections. At the time of filing, there was no demonstration that an *in vivo* infection of a *Tupaia belangeri* with HIV could be established and therefore the disease manifestations, if any, were not known. One of skill in the art would readily recognize that the claimed screening methods require the availability of an HIV-infected *Tupaia belangeri* that models human HIV disease. The art amply demonstrates, however, that intensive investigation has met with limited success in producing animal models that accurately reflect the human disease (see Lewis et al., 1995).

At page 8 of the response, Applicants assert that genetic modifications that could be made to render an individual *Tupaia belangeri* susceptible to infection by one of the human viral pathogens recited in the claims would be considered inoperative embodiments and Applicants cite the decision in *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) which states

that "the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort that is normally required in the art." Applicants further assert "in relation to the presence of inoperative embodiments … the utility and enablement of the claimed invention is not negated by whether or not the claims are enabled for a genetically engineered *Tupaia belangeri*, since such potentially inoperative embodiments would be understood as such by the skilled artisan" (sentence bridging pages 8-9 of the response). With regard to genetically modified tupaias (i.e., tupaias that have undergone genetic manipulations to enhance viral susceptibility), while such embodiments are not enabled by the instant application, there is no basis for alleging that they are inoperative embodiments. As shown in the prior art, the production of transgenic animals is a common approach in generating animal models of human infectious disease (see e.g. Lewis et al., 1995, page 149, section titled "Transgenic mice"). However, the production and characterization of such animals would clearly require undue experimentation to successfully produce an animal that could be used in the claimed screening methods. Furthermore, there is no evidence to suggest that one of skill in the art could determine which embodiments would be inoperative or operative without undue experimentation.

At page 8 of the response, Applicants assert that the instant specification describes infection of *Tupaia belangeri* for the first time with HBV and HIV, and the skilled artisan would understand that such infected *Tupaia belangeri* could be used to develop a therapeutic procedure for those infections. This is incorrect. The art rejections hereinbelow and in earlier Office actions (mailed 3/26/2004, 8/8/2007, and 6/24/2008) demonstrate that the instant specification is not the first disclosure of *Tupaia belangeri* infected with HBV. Moreover, the instant specification provides no description of the infection of *Tupaia belangeri* with HIV. Therefore it cannot be said that "the specification describes infection of *Tupaia belangeri* for the first time with HBV and HIV."

At the bottom of page 8 of the response, Applicants assert that this small animal model is cheaper and easier to maintain and has a shorter lifespan than other HIV animal models, and thus provide a useful alternative to those models. On the contrary, there is no basis for alleging that this animal model provides a 'useful alternative' over other HIV animal models, since there is no evidence that an *in vivo* infection of HIV can be established in *Tupaia belangeri*, and no evidence that such animals would exhibit disease manifestations that model the human disease, even if an HIV infection could be established in these animals. In order to provide a useful alternative, the claimed screening method requires a *Tupaia belangeri* that is actually infected with HIV and actually exhibits disease manifestations relevant to the human disease. Therefore, any assertions with regard to an animal that is cheaper, easier to maintain, and having a shorter lifespan than potential alternatives does not address the issue of enablement, which is based on a failure to provide HIV-infected animals that exhibit disease manifestations relevant to the human disease. The claimed screening methods cannot be carried out until HIV-infected *Tupaia belangeri* with disease manifestations relevant to the human disease are established and characterized. For reasons of record, undue experimentation would be required to produce such animals. The art amply demonstrates that there are considerable obstacles to be overcome in generating an animal model that exhibits one or more hallmarks of human HIV disease. Thus, in the absence of specific guidance for producing HIV-infected animals that exhibit analogous disease manifestations, the skilled artisan would have been required to engage in undue experimentation to practice the claimed methods over the full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39, 49, 51, and 75-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walter et al. (1996, Hepatology 24: 1-5).

Claim 39 is directed to a method for developing a therapeutic procedure in a model animal system comprising the steps of:

a) infecting a *Tupaia belangeri* with a human viral pathogen, wherein said pathogen is HIV or HBV;

b) carrying out a potential therapeutic procedure in said infected *Tupaia belangeri*; and

c) evaluating the effect of said potential therapeutic procedure on disease manifestations caused by said human viral pathogen in said infected animal.

Claim 49 is directed to a method for developing a therapeutic procedure which alleviates a clinical manifestation of a disease caused by a human viral pathogen, wherein said pathogen is HBV, comprising the steps of:

a) infecting a *Tupaia belangeri* with HBV;

b) carrying out a potential therapeutic procedure in said infected *Tupaia belangeri*; and

c) evaluating the effect of said potential therapeutic procedure on the clinical manifestation caused by said human viral pathogen.

Walter et al. (1996) disclose that *Tupaia belangeri* are susceptible to infection with hepatitis B virus (HBV). The reference notes that *Tupaias* are useful for the experimental analysis of various molecular and clinical aspects of HBV infection, as well as the evaluation of various antiviral strategies (abstract and page 5, column 1, paragraph 3 and Figure 3). The viral antigen HBsAg was detected in sera from infected animals (page 2, column 1, paragraph 6). Antibodies (anti-HBs and anti-HBe) were also detected in sera from infected animals (page 2, column 1, paragraph 4 and Figure 3). Following *in vivo* transduction of HBV DNA into *Tupaia* livers, the animals developed antibodies to HBcAg (anti-HBc) and HBsAg (anti-HBs), demonstrating transient viral antigen synthesis (page 2, column 1, paragraph 6).

Newborn tupaias were inoculated with infectious HBV DNA-positive patient serum and followed for the appearance of viral antigens or antibodies in serum (page 3, column 1, paragraph 2). HBsAg was detected in serum 2 to 4 weeks after infection, followed by the appearance of anti-HBc, anti-HBs, and anti-HBe (page 3, paragraph bridging columns 1-2 and Figure 3). Adult tupaias were also infected with HBV DNA-positive patient serum and rapidly developed anti-HBc, anti-HBs, and anti-HBe antibodies (page 3, column 2, paragraph 2). With regard to disease manifestations in the liver itself, the reference notes that HBcAg could be identified immunohistochemically in the nuclei of liver cells from infected tupaias (page 3, column 2, paragraph 4 and Figure 5). The abnormal liver sections reported in the reference are another marker of HBV infection (Figure 5). With regard to the detection of viral RNA, the authors note that *in situ* hybridization for the detection of HBV RNA would provide a more exact definition of HBV infection efficiency of *Tupaia* hepatocytes (page 4, column 2, paragraph 3).

Given the authors' suggestion to use HBV-infected *Tupaia belangeri* to develop antiviral therapies, it would have been obvious to one of skill in the art to infect a *Tupaia belangeri* with HBV, carry out a potential therapeutic procedure on the infected tupaia, and evaluate the effect of the therapeutic procedure on the disease manifestations already shown by Walter et al. to be characteristic of HBV-infected tupaias, in order to determine if the procedure provides a therapeutic benefit. The particular symptoms, effects, and clinical manifestations of HBV infection of humans are well known and it would be an obvious approach to investigate the well-known parameters associated with the disease caused by HBV. Additionally, the particular symptoms, effects, and clinical manifestations of HBV infection of tupaias were known in the art, as shown by Walter et al., and it would be an obvious approach, in testing therapies, to evaluate these known parameters associated with the disease caused by HBV in tupaias. A reasonable expectation of success would have been anticipated because Walter et al. had already determined the serological profiles of HBV-infected tupaias and one of skill in the art could readily carry out the same procedures to detect a viral protein (as set forth in Claim 77), such as HBsAg

or HBcAg, a serum antibody (as set forth in Claim 78), a viral RNA (as set forth in Claim 76), or an abnormal liver section (as set forth in Claim 51) before and after performance of the potential therapeutic procedure. As demonstrated by the reference, viral protein can be detected in both serum and liver tissue. With regard to viral RNA, Walter et al. specifically teaches that one of skill in the art could detect HBV RNA by *in situ* hybridization to provide a more exact definition of HBV infection efficiency of *Tupaia* hepatocytes (page 4, column 2, paragraph 3). A reasonable expectation of success would also have been anticipated because screening methods that employ animal model systems to identify therapies are well known in the art and are the preferred means for pre-clinical testing.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 39, 49, 51, and 75-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (1996, J. Cancer Res. Clin. Oncol. 122: 283-288).

Yan et al. (1996) disclose that *Tupaia belangeri* can be infected with human hepatitis B virus (HBV) by inoculation with human serum positive for HBV (abstract). Infection can be prevented by immunization with hepatitis B vaccine. Immunization is a therapeutic procedure and therefore it is evident that the authors recognized the animal model as being useful for testing therapies. The authors note that their results successfully establish tree shrews as a reliable and useful animal model for research on HBV infection (abstract and page 288, column 1). One of skill in the art would recognize that research on HBV infection includes the testing and development of therapeutic protocols. After inoculation with HBV serum, HBV markers were detected in sera and liver tissues (page 285, column 1 and Figures 1-3). HBV DNA, HBsAg, and HBeAg were detected in the sera of infected animals (page 285, column 1 and page 287, column 1, paragraph 2). Anti-HBc antibodies were also detected in the sera of infected animals (page 287, column 1, paragraph 2). Serum levels of alanine aminotransferase (ALT) were significantly

elevated in infected animals (page 285, column 1 and Table 4). HBsAg was also found in the cytoplasm of hepatocytes and HBcAg was found in the nucleus of hepatocytes (page 285, column 1 and Figures 1 and 2). HBV DNA was also detected in liver sections (page 285, column 1 and Figure 3). Abnormal liver sections are depicted in Figures 1-3. Spotty necrosis of liver cells and portal inflammation appeared in the liver biopsies from 17 of the infected animals (page 285, column 1). Successively generated HBV infection produced similar results, with elevated serum levels of ALT and intrahepatocytic HB antigen found in liver tissue samples (page 285, column 2). Moreover, various degrees of hepatitis alteration were found in liver tissue samples from infected animals (page 285, column 2). The reference points out that the presence of HBV DNA in liver tissues demonstrates that HBV can invade the liver cells of tupaias (page 287, column 2, paragraph 1).

Given the disclosure of Yan et al., it would have been obvious to use HBV-infected *Tupaia belangeri* to develop and test potential antiviral therapies. As such, it would have been obvious to one of skill in the art to infect a *Tupaia belangeri* with HBV, carry out a potential therapeutic procedure on the infected tupaia, and evaluate the effect of the therapeutic procedure on the various infection markers reported by Yan et al., including serum ALT levels, HB antigen, HBV DNA, anti-HB antibodies, and liver section abnormalities, including inflammation, to determine if the procedure is therapeutic. For example, since elevated ALT levels are a marker of liver damage, lower levels of ALT, as compared to ALT levels in untreated infected control animals, would indicate that the procedure is therapeutic. A reasonable expectation of success would have been anticipated because serum levels of ALT are a well-known marker of liver damage and screening methods that employ animal models of human diseases to identify therapies are well known in the art and are the preferred means for pre-clinical testing. In fact, the instant specification admits that the release of ALT from lysed hepatocytes into the plasma is a marker of hepatocyte death and indicative of liver injury. In particular, the specification notes that ALT levels in plasma are a standard measure of hepatocyte death and injury (paragraph bridging pages 13-14).

Nevertheless, the teachings of the specification are not relied upon for this rejection. The particular symptoms, effects, and clinical manifestations of HBV infection of humans are well known and it would be an obvious approach to evaluate the well-known parameters associated with the disease caused by HBV. Additionally, the particular symptoms, effects, and clinical manifestations of HBV infection of tupaias were known in the art, as shown by Yan et al., and it would be an obvious approach, in testing therapies, to evaluate these known parameters associated with the disease caused by HBV in tupaias. A reasonable expectation of success would have been anticipated in detecting any of the infection markers reported by Yan et al. because these markers were already shown to be characteristic of HBV infection in tupaias.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Yan et al. (1996, J. Cancer Res. Clin. Oncol. 122: 289-295) describe the development of hepatocellular carcinoma in *Tupaia belangeri* infected with HBV.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632